UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

CORCEPT THERAPEUTICS, INC., **Plaintiff,** **v.** **TEVA PHARMACEUTICALS USA, INC.,** **Defendant.**	Civil Action No. 18-3632 (RMB)(LDW) Hon. Renèe Marie Bumb, U.S.D.J. Hon. Leda Dunn Wettre, U.S.M.J. (**Filed Electronically**)

PLAINTIFF'S POST-TRIAL BRIEF

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Teva copied Corcept's Korlym label, including the express instructions to doctors to perform the patented methods. The experts agree that there is only one (infringing) set of dosing instructions in Teva's label for each of the three patient populations covered by the asserted claims,[1] and the evidence shows doctors will follow those instructions. This is sufficient to show future direct infringement. Moreover, the evidence ***outside*** the label confirms that doctors will directly infringe in the future, in spite of Teva's speculative reliance on osilodrostat.

The experts also agree Teva's label "recommends" the claimed dosing instructions be followed, which is sufficient to show Teva's intent. The evidence shows Teva's label goes even further, stating the claimed dosing instructions are "required" for the three patient populations at issue. This is not vague or speculative; Teva's label clearly directs doctors to infringe.

In response, Teva contorts the holdings of two recent cases (*Genentech* and *HZNP*) to argue that the law has changed and the Court should ignore the express instructions in Teva's label. As set forth herein, Teva's view of the law is incorrect, invites this Court to commit legal error, and should be rejected. Regardless, even under Teva's incorrect standards, the evidence presented at trial sufficiently demonstrates that Teva will induce future infringement.

I. BACKGROUND

Corcept's mifepristone product, Korlym, was approved in February 2012. PTX-12. Korlym is prescribed to around 1500 patients, and most receive doses of 900 or 1200 mg/day. Tr. 123:13-18; 147:4-6; PTX-051.107. Following Korlym's approval, Corcept undertook studies analyzing the interaction between strong CYP3A inhibitors and mifepristone, because FDA and Corcept "knew at that point that these drugs would be used together." Tr. 132:2-11; 137:5-17;

[1] I.e., Cushing's syndrome patients (1) already taking 900 mg mifepristone (claim 10 of the '214 patent); (2) already taking 1200 mg mifepristone (claim 1 of the '800 patent); and (3) already taking a strong CYP3A inhibitor (claim 6 of the '800 patent).

138:14-20; PTX-12.4. In view of doctors' desire to safely co-administer to the patients using higher doses, FDA and Corcept hoped the studies would "provide more therapeutic options . . . to Cushing's patients and appropriate labeling of mifepristone when co-administered with CYP3A inhibitors." Tr. 211:8-11; 143:21-145:7; PTX-49.2. That is exactly what happened.

Corcept, led by CEO Dr. Belanoff, ran a series of studies showing that, contrary to expectations, it was safe to administer high doses of mifepristone (up to 900 mg) with strong CYP3A inhibitors. Tr. 128:6-12; 131:16-132:1; 133:15-134:1; 151:1-8; 212:13-213:3. The study results led to the patents-in-suit and substantial changes to the Korlym label. Tr. 134:21-135:8; 152:1-23; JTX-16.16-17. The FDA found the results relevant to expanding clinical practice—in addition to including the results of the safety studies in section 12.3, the FDA: **(1)** added "a whole new section" (§ 2.5) to the "Dosage and Administration" portion of the label with explicit instructions on "Concomitant Administration with CYP3A Inhibitors" (Tr. 153:1-7; 214:5-16; JTX-16.4); **(2)** raised the maximum concomitant dose of mifepristone to 900 mg (Tr. 154:1-2; 215:9-11); and **(3)** removed the "extreme caution" warning about co-administration (Tr. 153:20-154:24; 214:17-216:3; JTX-16.6, 11). As Dr. Belanoff explained, these changes meant:

> [T]his large group of drugs, could now be safely combined with mifepristone, and, therefore, a larger group of patients who might not otherwise be able to be treated with mifepristone, which we really believe works, now could be. And the second part of it is that we could offer actual instructions that might be useful to a practitioner, that could be memorialized in the label, ***which they follow***.

Tr. 155:9-21. This testimony concerning the clinical import of FDA's approval of the safe and effective dosage instructions for co-administration was unrebutted.

II. CORCEPT PROVED THAT DIRECT INFRINGEMENT WILL OCCUR

A. The Expert Testimony Regarding Teva's Label *Alone* Provides Sufficient Evidence That Doctors Will Directly Infringe

In an induced-infringement case arising under the Hatch-Waxman Act, the Federal

Circuit has never "required evidence regarding the general prevalence of the induced activity." *Eli Lilly v. Teva Parenteral Medicines*, 845 F.3d 1357, 1368 (Fed. Cir. 2017). The Federal Circuit has held that "patentees in Hatch-Waxman litigations asserting method patents do not have to prove that prior use of the NDA-approved drug satisfies the limitations of the asserted claims." *Vanda Pharms. v. W.-Ward Pharms.*, 887 F.3d 1117, 1130 (Fed. Cir. 2018). Instead, a patentee can "satisfy its burden to prove the predicate direct infringement by showing that if the proposed ANDA product were marketed, it would infringe the [asserted] patent[s]." *Id.* According to the Federal Circuit, this showing may be made upon "factual findings that the proposed label 'recommends' that physicians perform the claimed steps." *Id.*

Here, the Court can find infringement based entirely on Teva's label and the expert testimony interpreting its instructions to recommend the claimed steps. At trial, the expert testimony was consistent and therefore dispositive—Teva's label recommends physicians perform the claimed steps when co-administering mifepristone with a strong CYP3A inhibitor in the relevant patient populations. Corcept's expert, Dr. Carroll, testified that of the three asserted independent claims, two (claim 10 of the '214 patent and claim 1 of the '800 patent) have similar steps. Tr. 219:1-15. Claim 10 requires administration of a reduced mifepristone dose (600 mg) to a patient who was taking an original mifepristone dose of 900 mg or 1200 mg with a strong CYP3A inhibitor. *Id.*; JTX-1.37. Claim 1 requires administration of a reduced mifepristone dose (900 mg) to a patient who was taking an original mifepristone dose of 1200 mg with a strong CYP3A inhibitor. *Id.*; JTX-3.41. The third asserted independent claim (claim 6 of the '800 patent) is structured differently and requires administering 900 mg of mifepristone to a patient who is already taking a strong CYP3A inhibitor. Tr. 224:25-225:5; JTX-3.41. Dr. Carroll testified that Teva's label instructs physicians to carry out each step of the claimed

methods. Tr. 219:18-224:10 (claims 10 and 1); Tr. 225:6-228:22 (claim 6).[2] He further specifically testified that physicians would follow the infringing instructions:

- *Claim 10 of the '214 Patent and Claim 1 of the '800 Patent*: "**Q**. In your opinion, Doctor, in instances where medical professionals determine that it is necessary to co-administer mifepristone and a strong CYP3A inhibitor to a patient who is already taking 1,200 mgs or 900 mgs of mifepristone, would medical professionals follow the instructions in Teva's label? **A**. Yes, they would."

- *Claim 6 of the '800 Patent*: "**Q**. In your opinion, Doctor, in instances where medical professionals determine that it is medically necessary to co-administer 900 mgs mifepristone to a patient taking one of the strong CYP3A inhibitors set forth in the claims, would medical professionals follow the instructions in Teva's label? **A**. Yes, they would."

See Tr. 223:24-224:4 (claims 10 and 1); Tr. 228:2-7 (claim 6). Dr. Carroll's opinion was clear: "The package insert from Teva recommends medical professionals to practice those claimed elements when medically necessary." Tr. 246:16-22; *see also* Tr. 218:17-23.

Teva's expert, Dr. Snyder, ***agreed*** that Teva's label recommends that the infringing dosage instructions be followed when co-administering to the relevant patient populations:

- *Claim 10 of the '214 Patent*: "**Q**. When a strong CYP3A inhibitor is added to a patient already being treated with mifepristone tablets, Teva's package insert recommends to doctors to adjust the dose of mifepristone according to Section 2.5, correct? **A**. The recommendations are in 2.5. **Q**. In the circumstances where the mifepristone original dose is 900 milligrams, Teva's label instructs the physician to reduce the dose to 600 milligrams? **A**. Yes. That's what it says."

- *Claim 1 of the '800 Patent*: "**Q**. When a healthcare professional administers a strong CYP3A inhibitor to a patient taking 1,200 milligrams of mifepristone, Teva's package insert instructs medical professionals to reduce the dose to 900 mg, correct? **A**. Yes. **Q**. Teva's package insert recommends reducing a 1,200- milligram mifepristone dose to 900 milligrams when adding a strong CYP3A inhibitor, correct? **A**. Yes."

- *Claim 6 of the '800 Patent*: "**Q**. In section 5.6, Teva's label recommends a maximal dose of 900 milligrams per day when mifepristone is used with strong CYP3A inhibitors,

[2] Teva's identification of certain patient populations that do not infringe is irrelevant since the label provides only infringing instructions for the three patient populations at issue. *See Sanofi v. Watson Labs.*, 875 F.3d 636, 644 (Fed. Cir. 2017) (explaining that Section 271(b) "does not contain the 'substantial noninfringing use' restriction … a person can be liable for inducing an infringing use of a product even if the product has substantial noninfringing uses.").

correct? **A**. I see that. **Q**. And you consider that a recommendation, correct? **A**. Yes." *See* Tr. 425:21-426:13 (claims 10 and 1); Tr. 427:6-12 (claim 6).

Based on the uniform expert testimony set forth above, the Court should find that Corcept has satisfied its burden of proving direct infringement. As the Federal Circuit has held, where a "district court [has] made factual findings that the proposed label 'recommends' that physicians perform the claimed steps, . . . its analysis of the proposed label to assess potential direct infringement by physicians [i]s proper under [Federal Circuit] precedent." *Vanda*, 887 F.3d at 1130. Accordingly and for this reason alone, Corcept has proven direct infringement.

B. The Real-World Evidence Further Supports Future Direct Infringement

Teva argues that *Genentech v. Sandoz*, 55 F.4th 1368 (Fed. Cir. 2022) changed the law to ***require*** the Court to go outside the label to assess past conduct of physicians to determine whether infringement is likely to occur in the future. Tr. 337-39. As an initial matter, the split three-judge *Genentech* panel could not have changed the law because Federal Circuit "panels do not have the authority to overrule prior precedential panel decisions." *Diamond Coating Techs. v. Hyundai Motor Am.*, 823 F.3d 615, 621 (Fed. Cir. 2016). Instead, in *Genentech*, the expert testimony interpreting the label at issue was insufficient by itself to show direct infringement, necessitating the court to consider evidence outside of the label.[3] The Federal Circuit has long held that if the ANDA "defin[es] a proposed generic drug in a manner that directly addresses the

[3] The accused label in *Genentech*—which was more restrictively worded than even the 2012 Korlym Label—stated that "concomitant administration" is "***not recommended***" and the "[u]se of fluvoxamine . . . should be ***discontinued*** prior to administration of pirfenidone and ***avoided*** during pirfenidone treatment." 55 F.4th at 1375. Because that label did "not recommend" infringement, the Court considered evidence beyond the label concerning past physician practice and found that "Genentech had not shown that any patient would be prescribed both pirfenidone and fluvoxamine." *Id*. Here, even though Teva's accused label did not have similarly restrictive language, Corcept submitted such extensive evidence of co-administration that the Court ultimately found that further evidence was cumulative. Tr. 463:6-464:2.

issue of infringement, [it] control[s] the infringement inquiry." *Par Pharm. v. Eagle Pharms.*, 44 F.4th 1379, 1383-84 (Fed. Cir. 2022) (alteration original) (citations omitted). Courts look to evidence outside the ANDA only if it "does not speak clearly and directly to the question of infringement." *Id.* Here, as discussed above, the testimony concerning Teva's label directly addresses infringement, and thus is dispositive. *See supra* § II.A. Nonetheless, while it is not necessary to reach the evidence outside of the label, that evidence also indisputably supports infringement under the preponderance of the evidence standard for the following reasons.

1. There Will Be Instances Where It Is Medically Necessary To Co-administer Mifepristone And Strong CYP3A Inhibitors

The evidence presented at trial establishes that for some patients with Cushing's syndrome, it is medically necessary to treat the manifestations or comorbidities of their disease with a combination of mifepristone and a strong CYP3A inhibitor. Tr. 130:9-25. While surgery to remove the tumor that causes hypercortisolism is the preferred treatment (Tr. 53:15-54:11), it is not always an option, which "leaves patients with a real problem because the excess cortisol activity by itself can be lethal over a period of time, and it has to be treated medicinally." Tr. 120:12-121:12; *see also* Tr. 54:12-55:3. Mifepristone is one such medicinal therapy. Tr. 121:5-12; 123:8-18. Ideally, mifepristone monotherapy (i.e., mifepristone administered without any other drug) is sufficient to efficaciously treat the patient. But there are patients so sickened by their disease that combination therapy with mifepristone and a CYP3A inhibitor becomes necessary "and the best choice." Tr. 131:3-6. As Dr. Belanoff explained:

> [i]deally, you would use only a single medication. . . . But there are some patients for whom that's just not going to get it done. And they're really the sickest patients, the most likely to have side effects, the most problematic patients to treat. That's where [two drugs] might actually end up getting combined.

Tr. 140:19-141:23. Thus, the answer to the Court's question regarding whether there is a reluctance to co-administer in view of the nature of the patients and interaction studies (Tr.

493:17-494:4)[4] is no. The evidence shows that there are several situations where co-administration has been necessary in the past and will remain necessary in the future.[5]

First, the strong CYP3A inhibitor ketoconazole remains the most commonly used medication to treat Cushing's syndrome. Tr. 240:6-11; 451:7-9; DTX-34.3. The evidence shows that for some patients with difficult-to-treat Cushing's syndrome, it has been necessary to co-administer mifepristone with ketoconazole due to their different and complementary mechanisms of action. Tr. 59:1-11. Mifepristone works by blocking cortisol from attaching to receptors, while ketoconazole works by inhibiting cortisol production. *Id.* Teva's expert Dr. Dobs testified that for some seriously ill patients, "it may be necessary to take advantage of mifepristone and ketoconazole's dual mechanisms of action." Tr. 59:12-18. Dr. Carroll agreed, explaining that:

> there are times when patients need more treatment than just one medication. So [they] need dual therapy. And in the case of ketoconazole and mifepristone, we have a medication, ketoconazole, that blocks the production of cortisol. And then we have mifepristone, a medication which blocks the effects. So we've lowered the levels with ketoconazole, and what's left around, we're blocking with mifepristone. So we have two different ways to get at the problem of too much cortisol activity.

Tr. 238:20-239:5. As discussed above, at the time of Korlym approval in 2012, in several documents, FDA recognized a "high potential" of concomitant use and a "likelihood" that co-administration of mifepristone and ketoconazole may be "necessary" to treat difficult cases of

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[4] It is of no moment that the studies were not carried out in seriously ill patients, because the FDA had found during the Korlym approval process that "***there is no significant difference in pharmacokinetics in healthy volunteers and patients***." JTX-005.415; *see also* PTX-051.31 (the "***findings in healthy volunteers are generally applicable to Cushing's syndrome patients***.") (emphases added). Further, Dr. Snyder agreed that such studies are "typically performed in healthy subjects." Tr. 405:11-14. The results from Corcept's studies appear in Teva's FDA-approved label (JTX-11), indicating to physicians that the FDA reviewed the data, "evaluated it," "thought it was safe," and found it relevant to clinical practice. Tr. 286:11-18; 419:17-420:8.

[5] Teva itself previously argued during a post-grant proceeding that there was a "high likelihood" of co-administration with strong CYP3A inhibitors. D.I. 277 at 2. Teva's new argument of the exact opposite should be given little weight. Tr. 108:9-14 ("To this Court's thinking, Teva seeks to have it both ways—'talks out of both sides'…").

Cushing's syndrome. PTX-49.1; Tr. 143:13-144:12; Tr. 243:4-244:4; PTX-012.4; PTX-51.16.

Following the approval of Korlym, the "high potential" recognized by the FDA has been realized in clinical practice. Dr. Dobs testified that in approximately half of the patients she has treated with mifepristone, she has found it necessary to co-administer ketoconazole. Tr. 57:11-14; 58:13-21. Dr. Dobs explained these were "extremely ill" patients and combination therapy was the "best choice for them." Tr. 58:22-25. A 2019 abstract reported on a woman "with rapidly progressive Cushing's syndrome" who was given ketoconazole and mifepristone and "showed improvements in her hypokalemia and glucose after mifepristone was started." Tr. 461:1-462:12. Another published case report describes an extremely ill patient treated just last year with the combination of mifepristone and ketoconazole. Tr. 244:25-245:14; PTX-053. As Dr. Carroll explained, it may be necessary to use combination therapy in these instances because:

> [T]hese are patients that are very, very sick. They need treatment. And in these instances, we're talking about somebody that just doesn't have efficacious therapy with one medication. They failed surgery. And we need to do everything that we can to treat those patients, and adding a synergistic medication would be … logical.

Tr. 241:4-13; 238:4-13. At bottom, the evidence shows that extremely ill patients have required, and will likely continue to require, combination therapy with ketoconazole and mifepristone.

Second, the evidence shows patients with Cushing's syndrome are immunosuppressed and develop opportunistic infections, including fungal infections, requiring combination therapy. Tr. 229:23-232:1 (citing PTX-15; PTX-16). Dr. Carroll testified aspergillus is one of the most common opportunistic infections afflicting persons with Cushing's syndrome, and the first-line treatment recommended by the CDC is itraconazole or voriconazole, which are strong CYP3A inhibitors. Tr. 232:18-235:17 (citing PTX-015; PTX-016; PTX-042). Even Dr. Snyder testified that, for invasive aspergillosis, UpToDate (JTX-22) teaches the first-line treatments are the strong CYP3A inhibitors voriconazole and posaconazole. Tr. 453:7-25. Dr. Carroll's opinion

was also informed by testimony of another endocrinologist (Dr. Hamrahian) who testified that he had co-administered mifepristone and a strong CYP3A inhibitor to treat a fungal infection. Tr. 236:22-238:2. Thus, it will remain necessary to co-administer mifepristone with a strong CYP3A inhibitor to a Cushing's syndrome patient battling a fungal infection. Tr. 235:18-236:6.

Third, the evidence shows that several of the claimed strong CYP3A inhibitors are medications that treat common conditions and manifestations of Cushing's syndrome such as depression, HIV, hepatitis, and bacterial infections. Tr. 129:3-131:6; 211:17-20; 397:7-16. Thus, for some patients, it will likely be both "necessary" and the "best choice" to treat certain manifestations of the disease using one of the claimed strong CYP3A inhibitors. *Id.*

2. When Medically Necessary, Doctors Will Co-administer Mifepristone And Strong CYP3A Inhibitors As Instructed By Teva's Label

Teva attempted to explain away past evidence of co-administration by asserting that there is no evidence that any past co-administration occurred at the claimed mifepristone doses. *See, e.g.*, Tr. 339. But the experts agree that the claimed dose adjustment steps are set forth in Teva's label and agree that Teva's label recommends that the claimed dose adjustment steps be followed for co-administration. Tr. 246:4-9; *Supra* § II.A. Accordingly, the only questions for these claims becomes whether it will ever be necessary to co-administer mifepristone and a strong CYP3A inhibitor to a patient already taking 900 or 1200 mg of mifepristone (Claims 1 and 10) or to administer 900 mg mifepristone to a patient taking a strong CYP3A inhibitor (Claim 6). The evidence answers these questions in the affirmative, and shows that there would not be a reluctance to co-administer mifepristone doses above 300 mg.

Claims 1 and 10. The evidence shows there is only one optimal mifepristone dose for any given patient. Tr. 146:25-147:4. And that optimal dose for the majority of patients is 900 or 1200 mg. Tr. 147:4-6; 320:23-321:2; PTX-051.107. Korlym and Teva's ANDA Product are

available as a single dosage form: a 300 mg tablet. *See* JTX-011.4 §3; JTX-016.4 §3. The labels for both products instruct that "[t]he recommended starting dose is 300 mg orally once daily," and that the dose "may be increased in 300 mg increments . . . to a maximum of 1,200 mg once daily." JTX-011.3; JTX-016.3. The labels further instruct that "[d]ecisions about dose increases should be based on a clinical assessment of tolerability and degree of improvement in Cushing's syndrome manifestations." *Id.* Doctors initiate therapy at 300 mg and then titrate ***every patient*** upward until the optimal dose is reached. Tr. 146:25-147:6; 331:4-18. Thus, the majority of the 1,500 patients currently being treated with Korlym (Tr. 123:13-18) are optimized to a dose of 900 or 1200 mg. PTX-051.107. When any one of these over 750 patients receives a 900 or 1200 mg dose and **(1)** requires ketoconazole to further control their Cushing's syndrome[6], **(2)** develops a fungal infection requiring treatment with itraconazole, voriconazole, or posaconazole, or **(3)** requires another strong CYP3A inhibitor for treatment of conditions such as depression, HIV, hepatitis, or bacterial infection (Tr. 129:3-131:6), all experts agree the labels recommends reducing mifepristone to an infringing dose. *Supra* § II.A. The label includes these dosing instructions to encourage the use of the higher doses of mifepristone with strong CYP3A inhibitors. Tr. 143:21-144:12. For example, Dr. Carroll testified that "in the future," if he had a patient where it was "medically necessary to take advantage of mifepristone and ketoconazole's dual mechanisms of action to reduce cortisol and bring a benefit to the patient," he ***will*** "co-

[6] Specifically with respect to claim 1, Teva's label instructs titrating to a maximum of 1200 mg based on an assessment of tolerability and efficacy, meaning, as Dr. Belanoff and Dr. Carroll explained, dose titration should increase "until they get to the optimal clinical outcome." Tr. 146:25-147:6; 331:4-18. Teva's label does not permit the doctor to increase the dose any higher for a patient that does not respond to 1200 mg—1500 mg is not an option. Teva's label instructs, however, that a doctor could reduce the 1200 mg mifepristone dose to 900 mg and co-administer ketoconazole (*see* JTX-011.4 at Table 1), which may "have added benefit" in treating Cushing's Syndrome through the medicines' dual mechanisms of action. *See* PTX-20.8; Tr. 59:12-18.

administer according to the instructions set forth in Teva's label." Tr. 246:4-9. This evidences a sufficient likelihood of direct infringement and no reluctance to use doses greater than 300 mg.[7]

Claim 6. The reasons above also apply to Claim 6, which requires administration of 900 mg mifepristone to a patient who is taking a strong CYP3A inhibitor. In instances where a patient comes to a doctor in need of mifepristone but is taking one of the claimed strong CYP3A inhibitors for any of the three scenarios above, Teva's label instructs doctors to start mifepristone at a 300 mg dose and then titrate to an infringing 900 mg dose if clinically indicated. Tr. 224:25-228:22; 154:16-24. And because most patients who receive mifepristone require doses of 900 mg or more to achieve efficacy (Tr. 146:25-147:6), physicians will titrate to 900 mg mifepristone for those patients taking a strong CYP3A inhibitor. Tr. 228:2-13. Again, that evidences a sufficient likelihood of direct infringement and no reluctance to use 900 mg.

3. Teva's Reliance On Osilodrostat Is A Red Herring

Teva and its expert have taken the position that future infringement is unlikely because physicians allegedly could avoid co-administering mifepristone and a strong CYP3A inhibitor "by using a drug other than mifepristone to treat the Cushing's syndrome, like osilodrostat." Tr. 407:4-17. This argument fails both legally and factually. Legally, Dr. Snyder undertook the wrong analysis by starting with the question of "how could one avoid co-administration[?]" *Id.* Unlike *Genentech*, Teva's label does not instruct doctors to "avoid" co-administration.

As a factual matter, Teva presented no evidence that Korlym has lost even a single prescription to osilodrostat, let alone that doctors are substituting osilodrostat in place of Korlym in instances where co-administration with a strong CYP3A inhibitor is necessary. To the

[7] That there is not a published case report evidencing the co-administration that is already occurring is not surprising. Tr. 244:9-13 (Dr. Carroll explaining that case reports are medical literature sharing "experience of treatment or diagnosis, usually of ***unique circumstances***.")

contrary, Dr. Belanoff testified that since the introduction of osilodrostat, Korlym sales have ***increased***. Tr. 123:20-125:1. Teva offered no rebuttal evidence.[8] And, although Dr. Snyder took the position (Tr. 410:18-411:10) that there have not been any instances of co-administration of mifepristone and a strong CYP3A inhibitor "since the introduction of osilodrostat" in 2020, that opinion is flatly contradicted by the evidence of record. *See* PTX-053; Tr. 487:22-488:10.

Moreover, the evidence shows that doctors would ***not*** substitute osilodrostat for mifepristone when adding a strong CYP3A inhibitor. ***First***, osilodrostat and mifepristone have different FDA-approved indications. Mifepristone is indicated to control certain manifestations of Cushing's ***syndrome***. Tr. 123:8-12; JTX-16.3 §1. Osilodrostat is indicated to treat Cushing's ***disease***. Tr. 474:2-23. Cushing's disease is limited to the subset of patients with Cushing's syndrome with a pituitary tumor. Tr. 52:22-53:2; 472:19-473:4. For the many patients whose Cushing's syndrome is caused by a tumor located anywhere else, osilodrostat is not an FDA-approved treatment—in other words, osilodrostat would not be an option for many patients on mifepristone. ***Second***, there is no reason why a doctor would substitute osilodrostat for mifepristone because osilodrostat's interaction with CYP3A inhibitors is even larger than mifepristone's interaction. Osilodrostat's label requires a two-fold greater dose reduction than Teva's mifepristone label[9]: the clinician must reduce the osilodrostat dosage ***by 50%*** because co-administration "may cause an increase in osilodrostat concentration and may increase the risk of [osilodrostat]-related adverse reactions." Tr. 475:6-476:10. In contrast, when co-administering a strong CYP3A inhibitor to a patient taking a 1200 mg mifepristone dose, the mifepristone dose

[8] Teva put forth no evidence of osilodrostat ever being administered with a strong CYP3A inhibitor, much less any evidence where a physician replaced mifepristone with osilodrostat because a strong CYP3A inhibitor was being administered.

[9] Notably, Dr. Snyder could not recall ever previously reading the label for osilodrostat—the product upon which Teva now relies for its non-infringement defense. Tr. 475:3-5.

need only be reduced ***by 25%***. *Id.*; JTX-11.4 ***Third***, the evidence shows that in difficult cases, doctors at times need to co-administer mifepristone with ketoconazole to take advantage of the drugs' dual (and complimentary) mechanisms. S*upra* § II.B.1. Osilodrostat, however, works the same way as ketoconazole—"by blocking the production of cortisol." Tr. 384:9-17. Thus, when a doctor needs to treat a difficult case by combining medications with ***different*** mechanisms, osilodrostat cannot be substituted for mifepristone. Tr. 58:22-59:11. ***Fourth***, Dr. Snyder cited sections of an "UpToDate" article on combination therapy in treating Cushing's syndrome, but those sections do not mention using osilodrostat as an alternative to mifepristone, much less with ketoconazole (or any other drug). DTX-34.8-9, 11.

Thus, the evidence shows osilodrostat is irrelevant to the concomitant use of mifepristone and strong CYP3A inhibitors.

III. CORCEPT PROVED THAT TEVA HAS THE SPECIFIC INTENT TO INDUCE INFRINGEMENT

A. Teva's Label Recommends Doctors Practice The Claimed Methods When Co-administering, Which Is Sufficient To Show Specific Intent

Turning to Teva's intent to induce infringement, the law that the Court must apply is clear: "[w]hen proof of specific intent depends on the label accompanying the marketing of a drug inducing infringement by physicians, '[t]he label must encourage, recommend, or promote infringement.'" *Vanda*, 887 F.3d at 1129; *see also Sanofi*, 875 F.3d at 644 (same). The law does not require that Teva's label encourage a doctor to decide *whether to use* mifepristone and a strong CYP3A inhibitor together; instead the "question" is "whether the instructions teach an infringing use *such that* we are willing to infer from those instructions an affirmative intent to infringe the patent." *Eli Lilly*, 845 F.3d at 1368. The Federal Circuit "has consistently held that, when a product is sold with an infringing label . . . such a label is evidence of intent to induce infringement." *GlaxoSmithKline v. Teva Pharms. USA*, 7 F.4th 1320, 1334 (Fed. Cir. 2021).

Teva's corporate witness explained that Teva "intends for physicians to prescribe its mifepristone product in accordance with [its label]." Tr. 73:11-23. And as set forth above, Dr. Carroll and Dr. Snyder agree that when it is necessary to: (1) co-administer a strong CYP3A inhibitor to a patient taking 900 mg mifepristone; (2) co-administer a strong CYP3A inhibitor to a patient taking 1200 mg mifepristone; or (3) co-administer mifepristone to a patient already taking a strong CYP3A inhibitor, Teva's label instructs and recommends that the physician follow infringing dosage adjustment steps. *Supra* § II.A; *see also* 440:16-25 (Dr. Snyder testifying that "Dose Adjustment Required" would instruct physicians to look at Section 2.5 of Teva's label.) That alone is sufficient evidence upon which the Court may enter a finding of induced infringement. *See, e.g.*, *AstraZeneca v. Apotex*, 633 F.3d 1042, 1060 (Fed. Cir. 2010) (inferring intent to induce infringement from a label that plainly "instructs users to perform the patented method."); *Braintree Labs. v. Breckenridge Pharm.*, 688 F. App'x 905, 910 (Fed. Cir. 2017) (when an "ANDA label 'instruct[s] how to engage in an infringing use, [it] show[s] an affirmative intent that the product be used to infringe.'").

Teva's attempt to escape its label is not supported by the case law. Teva argued at trial that its expert's admissions do not matter and its label does not recommend infringement because, while its label instructs "how to adjust the dose of mifepristone ***if*** you decide to co-administer the drug with a CYP3A inhibitor, . . . it doesn't tell you whether to co-administer the two drugs in the first place." Tr. 38. Teva characterizes its label as operating in an "if/then" manner, which it alleges is insufficient to enter a finding of induced infringement under *HZNP Medicines v. Actavis Labs. UT*, 940 F.3d 680 (Fed. Cir. 2019). Teva is wrong.

HZNP stands for the unremarkable proposition that inducement requires more than "describing" an infringing option:

> In ANDA cases, when a plaintiff attempts to draw intent from the label, we examine whether the proposed label "encourage[s], recommend[s], or promote[s] infringement." Merely describing the infringing use, or knowing of the possibility of infringement, will not suffice; specific intent and action to induce infringement must be shown.

Id. at 701-2 While *HZNP* characterized the "mere description" of the use as operating in an "if/then" manner, it did not elevate the words "*if/then*" into a magic incantation of non-infringement. The use of "if/then" was just shorthand to say that the *HZNP* label was permissive or optional.[10] Here, by contrast, Teva's label expressly acknowledges that there are instances when mifepristone is administered that "require" the claimed dosage adjustment steps be followed in order to treat patients co-administered a strong CYP3A inhibitor. *See* JTX-011.14 § 12.3; Tr. 217:19-218:5. As Dr. Carroll testified, the instances are medically necessary and the claimed dose adjustment steps are "required and not optional." *Id.*[11]

At bottom, *HZNP* did not create an "*if/then*" exception to induced infringement, nor does it require evidence that package inserts encourage doctors "whether" to administer any given drugs in the first place. Such an exception would preclude finding induced infringement for ***any*** method of treatment patent, as every single package insert could have an "if/then" interpretation—***if*** the physician (following his training and exercising his medical judgment)

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[10] The patents there claimed a method that had three steps: applying diclofenac sodium to the knee; waiting for the treated area to dry; and subsequently applying sunscreen or insect repellant to the treated area. The package insert instructed "if the user wants to cover the treated area with clothing or apply another substance over it, then the patient should wait until the area is dry." *See* 940 F.3d at 702. That instruction was deemed insufficient to induce, and key to the Court's finding was that it was entirely ***optional*** for the patient to perform the "*if*" step—i.e., nothing in the label recommended or required patients to cover the affected area with anything else, much less the ointments required by the claims. *See id.* at 700-701 (the label did not "require or direct, the post-product application of sunscreen, insect repellant, or a second topical medication.").

[11] Dr. Snyder previously agreed at his July 2023 deposition, but then recanted that testimony at trial, explaining only that his previous testimony had been a "mistake." Tr. 430:1-432:18. Corcept respectfully submits that the Court should not credit Dr. Snyder's newfound position. *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 493 F.3d 1368, 1381 (Fed. Cir. 2007).

chooses to administer a particular drug to treat a condition described in the package insert, ***then*** the physician should follow the instructions. This is not the law. Instead, the Federal Circuit has made clear numerous times over the past decade—since affirming this Court's decision in *AstraZeneca*—that courts are to consider whether the package insert instructs doctors to perform the patented method when they are using the generic drug. *See AstraZeneca*, 633 F.3d at 1060 ("The pertinent question is whether the proposed label instructs users to perform the patented method"); *accord Eli Lilly*, 845 F.3d at 1368-69 (the "question" is "whether the instructions teach an infringing use *such that* we are willing to infer from those instructions an affirmative intent to infringe the patent"); *Sanofi*, 875 F.3d at 646; *Braintree Labs*., 688 F. App'x at 910; *Vanda*, 887 F.3d at 1132. As the Court recognized during trial, "the only reason you're going to look at the label is because the physician has deemed it necessary to give the combination." Tr. 188:12-17. Teva's label indisputably instructs doctors to infringe. *See supra* § II.A.

A recent opinion from this District is directly on point. In *Janssen Pharms. v. Mylan Labs.*, the claimed methods related to a dosing regimen for reinitiating treatment with the drug paliperidone palmitate (which is typically dosed every three months) in patients who had missed their last dose within a four-to-nine-month window. *See* No. 20-13103, 2023 WL 3605733, at *7 (D.N.J. May 23, 2023). The defendant argued—just as Teva argues here—that its label would not induce infringement because, rather than encourage missed doses, the label included a "warning that missed doses should be avoided." *Id.* at *17. Judge Padin rejected that argument, ruling that although "the Proposed Labels discourage missed doses, [they] do not discourage or make optional the practice of the Asserted Claims (or any claimed steps) in the inevitable situation that doses ***are*** missed." *Id.* (emphasis in original). Judge Padin also distinguished *HZNP* because, in *HZNP*, "one of the claimed steps was optional," not recommended. *Id.*

Janssen is precisely applicable here. It confirms that the appropriate legal test is not whether the label recommends co-administration of any given drugs in the first place, but whether the label recommends infringement once the doctor has decided to give the drugs and consult the label. Thus, even if Teva's label suggests caution in co-administering mifepristone with strong CYP3A inhibitors unless medically necessary, and even if Teva's label does not state whether and when a strong CYP3A inhibitor should be co-administered, in the inevitable instances where it is medically necessary to co-administer, Teva's label does not "discourage or make optional the practice of the Asserted Claims." To the contrary, Teva's label expressly states that the claimed dosage adjustments are "required" in those instances, which physicians will view as non-optional instructions that must be followed in practice. Tr. 217:19-218:5.

For these reasons alone, the Court may find that Teva will induce infringement.

B. Teva's Label Actively Encourages Co-administration In Any Event

While not required, Corcept also proved that Teva's label encourages doctors "whether" to co-administer in the first place. There is no dispute that prior to the claimed inventions (e.g., in 2012), doctors ***desired*** to co-administer mifepristone with strong CYP3A inhibitors. Tr. 211:8-11; PTX-049.1; Tr. 143:13-144:12. But doctors did not think these drugs could safely be combined. Tr. 211:21-212:7; 146:8-22; 178:2-9.

After Corcept invented the claimed methods, the FDA expanded the 2019 Korlym label to include (a) data from the underlying clinical trials showing that the drugs could be co-administered safely, and (b) dosing instructions that directly read on the claimed methods. *See* Tr. 213:17-218:5 (Dr. Carroll explaining differences between the old and the current label). Dr. Belanoff testified that Corcept carried out the safety studies because it was important "to encourage people" to use combination therapy when needed. Tr. 143:21-144:12. Dr. Belanoff further explained that once he discovered how to safely combine mifepristone with strong

CYP3A inhibitors, the FDA amended the labelling to specifically "offer actual instructions that might be useful to a practitioner." Tr. 155:12-21. As Dr. Carroll testified, doctors wanted to co-administer but had been discouraged from doing so by the 2012 Korlym label; by contrast, the 2019 label, replete with safety data and new dosing instructions, now instructs and encourages physicians to co-administer. Tr. 246:16-247:17. As a doctor reviewing the updated label, Dr. Carroll is now "able to infer that co-administration of mifepristone and ketoconazole is ***safe*** and ***effective***." Tr. 303:1-8; 329:7-24. That encourages co-administration in the first place.

Teva attempts to refute this evidence with testimony from Dr. Snyder that, instead of encouraging co-administration, Teva's label makes him "very afraid" of co-administering. Tr. 394:8-11. Dr. Snyder's opinions regarding encouragement are not credible and should be given no weight. He does not believe that Teva's label even encourages the administration of mifepristone by itself. Tr. 420:16-421:11. He also does not believe there is any reason or need to ***ever*** prescribe mifepristone (Tr. 464:10-14, 466:21-467:1); his bias is belied by the fact that Teva took this case to trial to bring its mifepristone product into a market expected to be worth over $400 million dollars this year alone. Tr. 197:9-15. When asked how he could square his opinions with the evidence, Dr. Snyder simply responded, "you got me." Tr. 466:21-467:1. Further, Dr. Snyder's "be afraid" opinion is premised on the notion that mifepristone blood levels "can rise" in instances of co-administration with a strong CYP3A inhibitor. Tr. 395:2-17. Dr. Snyder agreed, however, that Table 3 of Teva's label reports only a 10-38% increase in mifepristone blood levels when co-administered; in contrast, a different drug that Teva's label ***contraindicates*** (simvastatin) showed a 1800% increase in blood levels. Tr. 444:1-445:10. Moreover, Dr. Snyder testified that he did not "know the clinical significance" of the mifepristone blood level data reported in Table 3. *Id.* Therefore, the only credible evidence of

record on the clinical significance of that mifepristone blood level data comes from Dr. Carroll and Dr. Belanoff, who offered unrebutted testimony that the mifepristone blood level data in Table 3 indicates to physicians that co-administration is safe. Tr. 217:13-18; 247:5-13; 128:6-12. Therefore, Dr. Snyder's supposed fear is unsupported by the record.[12]

The weight of the evidence shows that the clinical data and dosing instructions set forth in the Teva label would encourage a physician to co-administer in the first instance. Courts have routinely found data and dosing instructions to encourage infringement. *See, e.g.*, *Vanda*, 887 F.3d at 1131 (finding encouragement to induce where data in the label "constitutes a recommendation"); *Amarin Pharma v. Hikma Pharm.*, 449 F. Supp. 3d 967, 1000 (D. Nev. 2020) (finding encouragement where clinical trial data would recommend to "doctors to prescribe the applicable drug in [an infringing manner]."); *Salix Pharm. v. Norwich Pharm.*, No. 20-430, 2022 WL 3225381 at *12 (D. Del. Aug. 10, 2022) (holding that data in the label "will likely encourage some physicians to [practice the claimed methods].") The Court should find the same here.

C. Teva's Inducement Argument Does Not Apply to Claim 6

Teva's presentation at trial largely failed to distinguish between the three asserted independent claims. And while claim 10 of the '214 patent and claim 1 of the '800 patent are similarly structured, claim 6 is quite different. As Dr. Carroll explained, claim 6 just "requires ***one active step*** of administering 900 milligrams of mifepristone [to] a patient who's already taking a strong CYP3A inhibitor."[13] Tr. 224:25-225:5. To infringe claim 6, all one must do is

[12] Dr. Snyder's supposed fear is also legally irrelevant to inducement. *See Eli Lilly*, 845 F.3d at 1368-69 ("[W]e held in *AstraZeneca* that a label that instructed users to follow the instructions in an infringing manner was sufficient even though some users would not follow the instructions.").

[13] *See Janssen*, 2023 WL 3605733 at *14 ("It is important to remember that the elements, or the body, of a method claim are method steps, which should usually be verbal (gerundial) phrase, introduced by a gerund or verbal noun (the '-ing' form of a verb)"). Accordingly, only "administer***ing**" 900 mg of mifepristone needs to be encouraged for infringement of claim 6.

administer 900 mg mifepristone to a person who is already taking a strong CYP3A inhibitor. *See id.* Thus, even if the Court finds that Corcept must "encourage co-administration in the first place" to show inducement of claims 10 and 1, no such encouragement is needed for claim 6; Teva's label need only encourage a doctor to prescribe 900 mg mifepristone to a patient who shows up already taking a strong CYP3A inhibitor (perhaps from a different doctor). The evidence shows that the data and dosing instructions in Teva's label do just that. Tr. 488:14-18 (Snyder); Tr. 246:16-24 (Carroll). Thus, Teva induces infringement of claim 6.

D. Teva's Intent Is Also Evidenced By Its Failure to Seek Alternative Labeling

Finally, Teva and its expert argued that despite the recommendations in the label, mifepristone is such a dangerous drug that physicians would be "afraid" to combine it with a strong CYP3A inhibitor (if they prescribe mifepristone at all). But had Teva actually believed this, it could have petitioned the FDA to allow Teva to revert back to the original, more restrictive, 2012 Korlym label.[14] Its likelihood of success is irrelevant; as this Court has recognized, "a party should be required to attempt reconciliation [between patent laws and FDA regulations] by exhausting all regulatory avenues available." *AstraZeneca v. Apotex*, 623 F. Supp. 2d 615, 618 (D.N.J. 2009). That Teva did not even try (Tr. 426:24-427:5; 428-16:24) further evidences that Teva intends for its product to be co-administered in an infringing manner.

IV. CONCLUSION

For the reasons set forth herein, the evidence at trial showed by at least a preponderance of the evidence that Teva will induce infringement of the asserted claims.

[14] The FDA has allowed generic applicants to revert back to original labels of branded drugs. *See, e.g.,* FDA Docket No. 2008-P-0069-0010 at 10 (generic labeling would be allowed where it was "essentially the same as the labeling with which Camptosar was originally approved [because] Camptosar was safely marketed with only this labeling for approximately 4 years.").

Dated: October 26, 2023

Respectfully submitted,

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